IN THE CLAIMS

Please amend claims 49 and 50 as follows:

1-20 (Cancelled)

21. (Previously Presented) A hatched chimeric chicken comprised of progeny of embryonic stem cells having a genome comprising a stably integrated transgene wherein expression of the stably integrated transgene is detected in at least one tissue type of the chimeric chicken.

22-25 (Cancelled)

26. (Previously Presented) The chimeric chicken of claim 21 wherein the expression of the stably integrated transgene is detected in extra-embryonic tissue.

27. (Previously Presented) The chimeric chicken of claim 21 wherein the expression of the stably integrated transgene is detected in somatic tissue of the chicken.

28. (Previously Presented) The chimeric chicken of claim 27 wherein the somatic tissue is endodermal.

29. (Previously Presented) The chimeric chicken of claim 27 wherein the somatic tissue is mesodermal.

30. (Previously Presented) The chimeric chicken of claim 21 wherein the mesodermal tissue is lymphocytes of the chicken.

31-40 (Cancelled)

41. (Previously Presented) A method of creating a chimeric chicken comprising:

selecting chicken embryonic stem cells having a genome comprising a stably integrated transgene from a culture sustained for more than 60 days,

injecting the embryonic stem cells into a recipient embryo, and

hatching a chimeric chicken from the recipient embryo wherein expression of the stably integrated transgene is detected in at least one tissue type of the chimeric chicken.

42. (Previously Presented) The method of claim 41 wherein the injecting step is comprised of injecting embryonic stem cells into a compromised embryo.

43. (Previously Presented) The method of claim 42 wherein the embryo is compromised by gamma irradiation.

44. (Previously Presented) The method of claim 42 wherein the embryo is compromised by mechanical removal of cells from the embryo.

45. (Previously Presented) The method of claim 41 wherein the expression of the stably integrated transgene is detected in extra-embryonic tissue.

46. (Previously Presented) The method of claim 41 wherein the expression of the stably integrated transgene is detected in somatic tissue.

47. (Previously Presented) The method of claim 46 wherein the somatic tissue is ectodermal.

48. (Previously Presented) The method of claim 46 wherein the tissue is endodermal.

4951. (Currently Amended) The method of claim 46 wherein the tissue is mesodermal.

5052. (Currently Amended) The chimeric chicken of claim 27 wherein somatic tissue is ectodermal.

The present amendment responds to the issues raised in the final action in the pending application. A single remaining rejection is of record – a § 103 rejection based on the combination of the Pain et al. (1996) paper and the Gibbins et al. (1990) reference. The withdrawal of the rejection is necessary because the Examiner's interpretation of the Pain et al. and Gibbins et al. references on which the rejection is based, is demonstrably in error. Furthermore, the Examiner has asserted the existence of long-term cell cultures and the existence of chimeric birds that encode a transgene. No such composition or animal exists in the prior art and this basis for the § 103 rejection cannot be maintained.

The sole remaining rejection to the pending claims is based on the Examiner's reliance on an isolated statement in Pain et al (1996) that: "Regardless of the number of passages, more than 50% of the hatched recipient embryos were chimeras with nearly 33% of the plumage from donor phenotype". (page 2344 col 2 para 2). This is clearly a misquotation because the statement modifies the sentence above which states "Cells were collected from cultures after 1-3 passages". Hence, the meaning of the sentence is clearly that within the first three passages, chimeras could be produced. The final statement of the paragraph says: "The ability of long-term cultures to give rise to chimeric animals is currently under investigation". Clearly, chimeras could not be made from cells that had been in culture for longer than 19 days as is explicitly stated in the caption to Figure 8 of the reference.

Furthermore, because the legend for Fig. 8 says "...chimeric chicks derived from White Leghorn embryos grafted with Barred Rock CEC cultivated during 3 to 19 days," there can be no evidence that chicken ES cells could be cultivated for periods sufficient long to establish a stably transfected line of ES cells. Again, the final statement of the paragraph says: "The ability of long-term cultures to give rise to chimeric animals is currently under investigation." At that time, chimeras could not be made from

cells that had been in culture for long periods. The art does not contain any example of ES cells stably transfected with a transgene.

To summarize, the Pain et al (1996) paper teaches a culture containing cells which could produce chimeras, within 3 passages, when maintained in culture for 19 days or less -- characteristics that are shared with mouse ES and EC cells. For a short period of time (i.e. up to 19 days) they would make somatic chimeras and for 7 days they would make germline chimeras. However, after longer periods in culture, they would make neither somatic nor germline chimeras. All of these attributes are described in the paper and stand in sharp contrast to the interpretation of the examiner.

Gibbins et al. (1990) does not disclose selection of stably transfected cells nor the production of chimeras from these cells. Gibbins et al. (1990) specifically discloses that the goal has yet to be achieved. Gibbins et al. (1990) state:

> "A major problem that we have encountered is that we have not been successful in culturing chicken embryonic stem cells for any extended period of time without differentiation taking place."

Thus, genetically modified stem cells necessary to make the invention do not exist and the Examiner's proposition that the teaching of Pain establishes ES cells genetically modified stem cells (per Gibbins) cannot stand because Gibbins did not, and could not, produce genetically modified cells because the culture could not be maintained "for any extended period of time" such that transfection and selection take place.

As recently as 2004, researchers in the field of avian pluripotent stem cells described attempts to make chimeras from embryonic stem cells in culture and did not report the creation of chimeras from any culture longer than 20 days. Petitte et al. *Mechanisms of Development 121:* 1159-68 (2004) (attached), see Table 1.

The Examiner cannot legitimately contend that a reasonable expectation of success exists when the entire body of prior art cited by applicants and the Office reveal numerous failed attempts to create chimeras from cells held in long-term culture and do not reveal a single example beyond 20 days – even as recently as this year. The claimed method is the only successful creation of a chimera from a cell culture greater than 60 days old.

The Examiner also cannot maintain that the claimed chimeric chicken is indistinguishable from the prior art, because prior art chimeras do not have a stably integrated transgene. The Examiner has not, and cannot, cite an example in the prior art of a chimera having a transgene because none existed prior to the present invention.

The Examiner's rejection of the facts established by the Etches declaration cannot stand because the rejection is based on the same misinterpretation of the Pain et al. paper. The statement that Pain et al "clearly teaches in-vivo differentiation of chicken embryo cells ... for up to 60 days[.]" is directly contradicted by the express language of the paper where the maximum length of 19 days is disclosed.

Applicants contend that the pending claims are in condition for allowance and request such action accordingly.

Respectfully submitted,

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